Effect Modification of Long#Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women

ORIGINAL RESEARCH

Effect Modification of Long-Term Air Pollution Exposures and the Risk of Incident Cardiovascular Disease in US Women

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***Background*—**Ambient air pollution exposures have been frequently linked to cardiovascular disease (CVD) morbidity and mortality. However, less is known about the populations most susceptible to these adverse effects.

***Methods and Results*—**We assessed the associations of long-term particulate matter (PM) exposures with incident CVD in a nationwide cohort of 114 537 women in the Nurses' Health Study, and performed analyses to identify subpopulations at the greatest risk. Residential address level time-varying monthly exposures to $PM_{2.5}$, PM_{10}, and $PM_{2.5\ to\ 10}$ microns in diameter were estimated from spatio-temporal prediction models. In multivariable models, increases in all size fractions of PM were associated with small, but not statistically significant, increased risks of total CVD, coronary heart disease, and stroke. PM-associated CVD risks were statistically significantly higher among women with diabetes as compared to those without (*P*-for-interaction <0.0001 for PM_{10} and $PM_{2.5}$ and 0.007 for $PM_{2.5\ to\ 10}$). For each 10 $\mu g/m^3$ increase in 12-month average $PM_{2.5}$, $PM_{2.5\ to\ 10}$, and PM_{10}, the multivariable adjusted hazard ratios were 1.44 (95% CI: 1.23 to 1.68), 1.17 (95% CI: 1.05 to 1.30), and 1.19 (95% CI: 1.10 to 1.28) among women with diabetes. There were also suggestions of higher risks among older (≥70 years) women, the obese, and those living in the Northeast and South. Smoking status and family history did not consistently modify the association between PM and CVD, and risks were most elevated with exposures in the previous 12 months.

***Conclusions*—**In this nationwide cohort, women with diabetes were identified as the subpopulation most sensitive to the adverse cardiovascular health effects of PM. **(*J Am Heart Assoc*. 2015;4:e002301 doi: 10.1161/JAHA.115.002301)**

Key Words: air pollution • cardiovascular disease • effect modification • environment • myocardial infarction • stroke

A large body of evidence has formed implicating long-term exposures to particulate matter (PM) air pollution with an increased risk of cardiovascular disease (CVD) morbidity and mortality,[1,2] leading to the recognition of air pollution as a major risk factor for these outcomes.[3,4] For example, as part of the Global Burden of Disease 2010 project, ambient PM exposure was estimated to be responsible for 1.5 million ischemic heart disease deaths in 2010 with population-attributable fractions of 2% to 41%, depending on the country.[5] In a recent review of the evidence from long-term studies, each 10 $\mu g/m^3$ increase in PM <2.5 microns in aerodynamic diameter ($PM_{2.5}$) was associated with an 11% (95% CI: 5 to 16) increased risk of cardiovascular mortality.[2] Although the majority of studies have observed elevated risks with PM exposures, statistically significant heterogeneity in these estimates has been observed, even within studies.[6–9] Differences in the prevalence of risk factors and different proportions of susceptible subpopulations may underlie this heterogeneity. Therefore, the subpopulations at the greatest risk remain a key question in the literature.

Among women in the Nurses' Health Study (NHS) living in the Northeastern and Midwestern regions of the United States 1992–2002, we have previously observed an increased risk of incident overall coronary heart disease (CHD), fatal CHD, and nonfatal myocardial infarctions (MI) with increasing long-term exposures to $PM_{2.5}$, and evidence of heterogeneity by personal characteristics.[10] Our current objectives are to spatially (to the full contiguous United States) and temporally (1989–2006) expand our examination of these associations, to determine whether there is heterogeneity in effect esti-

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Table 1. Selected Age-Standardized Characteristics of Nurses' Health Study Participants Throughout the Full Period of Follow-Up (1989–2006) and After 2000

Characteristics, Mean (SD) or %	Follow-Up Period	
	1989–2006	2000–2006
N	114 537	96 058
Age, y*	63.5 (8.5)	68.6 (7.3)
Body mass index, kg/m^2	25.3 (7.6)	25.6 (7.5)
Body mass index categories		
Underweight/normal	43	41
Overweight	32	33
Obese	20	22
Race		
White	94	94
Black	2	2
Other/multiple races	6	6
Pack-years of smoking†	24.0 (21.1)	23.6 (21.4)
Smoking status		
Never	44	45
Former	42	45
Current	14	11
Menopause status		
Premenopausal	8	8
Postmenopausal	86	84
Dubious	5	4
Family history of myocardial infarction	33	32
Diabetes	8	9
Marital status		
Married	63	64
Not married	37	36
Region of residence		
Northeast	51	50
Midwest	17	17
West	14	14
South	18	19
Census tract median income ($1000)	63.9 (25.0)	63.4 (24.3)
Census tract median home value ($10 000)	17.2 (12.9)	17.2 (12.6)
12-month average exposure*		
PM_{10}	22.2 (6.5)	19.3 (5.4)
$PM_{2.5–10}$	8.7 (4.5)	7.3 (4.1)
$PM_{2.5}$	13.4 (3.3)	12.0 (2.8)

PM indicates particulate matter.
*Not age standardized.
†Among ever smokers only.

mates by region of the country or by personal characteristics including cardiovascular risk factors, to compare heterogeneity in effects across PM size fractions, and to assess the impact of these exposures on the risk of incident stroke, in addition to incident CHD.

Methods

Study Population

The NHS is a prospective cohort study of nurses started in 1976. At enrollment, the 121 701 women were 30 to 55 years of age, married, and completed a mailed questionnaire with detailed information on demographics, lifestyle characteristics, and prevalence of a number of diseases. Women were initially enrolled from a selection of 11 states; however, participants now live throughout the contiguous United States. Follow-up questionnaires are mailed every 2 years to update risk factor and disease status, and response rates have been consistently over 90%. All residential address locations have been geocoded to obtain longitude and latitude. Women were included in the current analyses if they remained alive and free of CVD through 1988, were still responding to questionnaires, and had at least a single address within the contiguous United States during 1988–2006 where air pollution predictions were available. The study protocol was approved by the Brigham and Women's Hospital Institutional Review Board, and consent was implied through the return of the questionnaires.

Outcome Assessment

On the baseline and all subsequent follow-up questionnaires, participants were asked to report all occurrences of physician diagnosed CVD, specifically, incidence of CHD or stroke. Women (or for fatal cases, next-of-kin) were asked to provide consent to review all medical records pertaining to their diagnosis. Cases of fatal CHD (ICD-8 and ICD-9 codes 410 to 412, ICD-10 codes I21 to I22) were classified as definite if confirmed by hospital records or through an autopsy, or if CHD was the most plausible cause of death and there was prior evidence of CHD. Cases were classified as probable if medical records surrounding the death were not available, but CHD was the underlying cause on the death certificate, National Death Index search, or a family member provided supporting information. Nonfatal MI was classified as definite if the criteria of the World Health Organization were met, specifically, symptoms and either electrocardiograph-detected changes or elevated cardiac-enzyme concentrations. Cases of nonfatal MIs were designated as probable if an interview or letter confirming hospitalization for the infarction was obtained and medical records were unavailable. Overall incident CHD was determined based on the first occurrence of

Table 2. HRs and 95% CI for a 10 μg/m^3 Increase in 12-Month Average PM With Risk of Incident CVD, CHD, or Stroke in the Nurses' Health Study

Outcome	Cases	Person-Years	PM_{10}		$PM_{2.5-10}$		$PM_{2.5}$	
			Basic*	Multivariable†	Basic*	Multivariable†	Basic*	Multivariable†
1989–2006 (N=114 537)								
Incident CVD	6767	1 835 486	1.05 (1.01–1.10)‡	1.02 (0.97–1.06)	1.11 (1.03–1.19)‡	1.03 (0.96–1.11)	1.04 (0.96–1.13)	1.02 (0.94–1.10)
Incident CHD	3878	1 835 486	1.06 (0.99–1.12)	1.01 (0.95–1.07)	1.12 (1.02–1.23)‡	1.03 (0.93–1.13)	1.02 (0.92–1.14)	0.99 (0.88–1.10)
Incident stroke	3295	1 835 486	1.05 (0.99–1.12)	1.03 (0.97–1.10)	1.11 (1.00–1.22)‡	1.05 (0.95–1.16)	1.03 (0.92–1.16)	1.03 (0.92–1.15)
2000–2006 (N=96 058)								
Incident CVD	2413	557 741	1.07 (0.98–1.16)	1.05 (0.96–1.14)	1.07 (0.95–1.21)	1.02 (0.90–1.16)	1.11 (0.96–1.28)	1.11 (0.96–1.29)
Incident CHD	1301	557 741	1.06 (0.94–1.19)	1.02 (0.91–1.15)	1.08 (0.91–1.28)	1.01 (0.85–1.19)	1.08 (0.88–1.32)	1.05 (0.86–1.29)
Incident stroke	1194	557 741	1.07 (0.96–1.21)	1.07 (0.95–1.20)	1.07 (0.90–1.27)	1.03 (0.87–1.23)	1.14 (0.93–1.40)	1.18 (0.96–1.45)

BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HRs, hazard ratios; MI, myocardial infarction; PM, particulate matter; SES, socioeconomic status.
*Adjusted for age, time period, region, and season.
†Additionally adjusted for race, smoking status and pack-years, BMI, menopausal status and hormone use, hypercholesterolemia, hypertension, diabetes, family history of MI, and individual- and area-level SES.
‡*P*-value <0.05.

either nonfatal MI or fatal CHD. Incident strokes were confirmed if characterized by a typical neurological defect of sudden or rapid onset, lasting more than 24 hours and attributable to a cerebrovascular event. Strokes were classified according to the criteria of the National Survey of Stroke as due to ischemia (embolic or thrombotic), hemorrhage

Table 3. Pearson Correlations Between All of the Exposure Averaging Periods Considered, 2000–2006

	12-Month			24-Month			60-Month			120-Month		
	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$
12-month												
PM_{10}	1.00	0.86	0.67	0.99	0.85	0.67	0.96	0.84	0.65	0.93	0.85	0.61
$PM_{2.5-10}$		1.00	0.20	0.85	0.99	0.21	0.82	0.97	0.21	0.77	0.93	0.18
$PM_{2.5}$			1.00	0.65	0.20	0.98	0.65	0.21	0.95	0.67	0.28	0.91
24-month												
PM_{10}				1.00	0.86	0.68	0.98	0.86	0.66	0.95	0.87	0.62
$PM_{2.5-10}$					1.00	0.22	0.84	0.98	0.22	0.78	0.95	0.19
$PM_{2.5}$						1.00	0.68	0.24	0.97	0.70	0.30	0.93
60-month												
PM_{10}							1.00	0.87	0.70	0.98	0.88	0.66
$PM_{2.5-10}$								1.00	0.24	0.82	0.98	0.21
$PM_{2.5}$									1.00	0.72	0.30	0.97
120-month												
PM_{10}										1.00	0.87	0.72
$PM_{2.5-10}$											1.00	0.28
$PM_{2.5}$												1.00

PM indicates particulate matter.

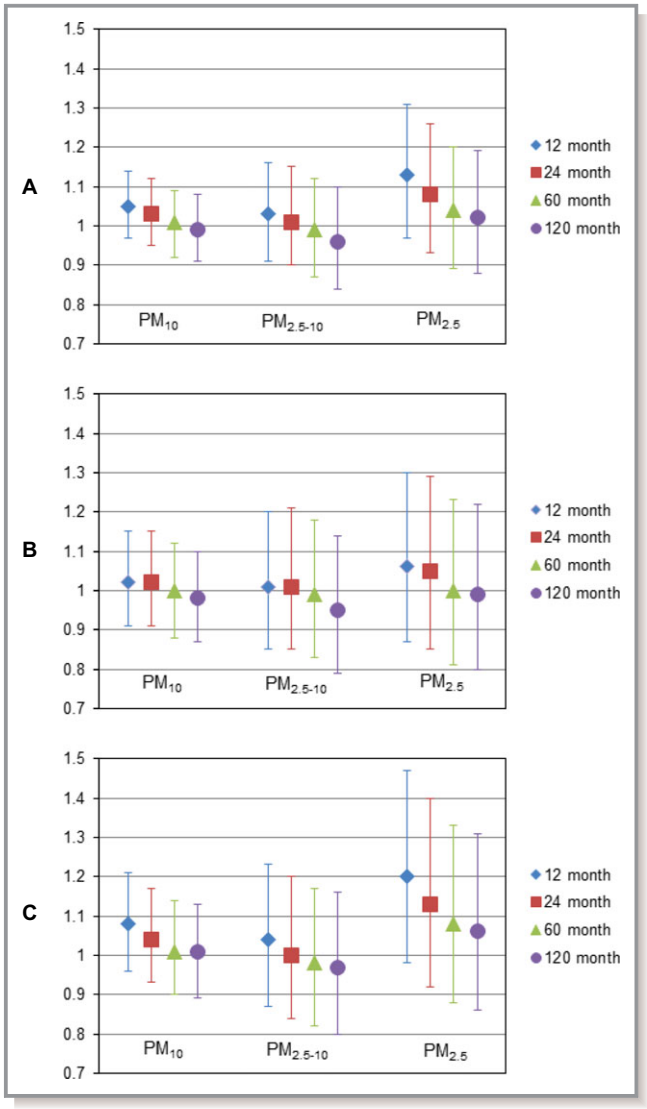

Figure. Multivariable associations for each 10 μg/m^3 increase in time-varying 12-, 24-, 60-, or 120-month particulate matter exposure with risk of total CVD (A), total CHD (B), or total stroke (C) 2000–2006. CHD indicates coronary heart disease; CVD, cardiovascular disease; PM, particulate matter.

(subarachnoid hemorrhage or intracerebral hemorrhage), or unknown cause.[11] Nonfatal strokes were designated as probable when the nurse provided additional information by interview or letter, but no medical records were available.

Exposure Assessment

Ambient predictions of $PM_{2.5}$ and PM <10 μm in aerodynamic diameter (PM_{10}) were available from spatio-temporal prediction models for all months between January 1988 and June 2006 for each residential address in the contiguous United States.[12] The models used monthly average $PM_{2.5}$ and/or PM_{10} monitoring data from the US Environmental Protection Agency's Air Quality System, the IMPROVE network, and other sources and the addresses were updated every 2 years.[13,14] Generalized additive mixed models incorporated these measured values with monthly spatial terms, geospatial predictors (including a number of potential sources, meteorology, and topology), and terms for time to create separate PM prediction surfaces for each month and each PM size fraction.[12] Since monitoring data on $PM_{2.5}$ were limited prior to 1999, $PM_{2.5}$ in the period before 1999 was modeled using data on PM_{10} and information on the ratio of PM_{10} to $PM_{2.5}$ in each location.[12] $PM_{2.5-10}$ was calculated by subtraction of the monthly PM_{10} and $PM_{2.5}$ estimates. Cross-validation results demonstrated that the models had high predictive accuracy (cross-validation R^2 values of 0.59, 0.76, and 0.77 for PM_{10}, pre-1999 $PM_{2.5}$, and post-1999 $PM_{2.5}$, respectively).[12]

Potential Confounders and Effect Modifiers

Information on potential confounders and effect modifiers is available every 2 years (every 4 years for diet information) from the follow-up questionnaires. Therefore, when appropriate, each woman was assigned updated covariate values for each questionnaire cycle. We included a number of risk factors for CVD or predictors of exposure as possible confounders including: age, race, calendar year, season, body mass index (BMI; kg/m^2), menopausal status and hormone use, comorbidities (hypertension, hypercholesterolemia, and type 2 diabetes), and family history of MI. Pack-years of smoking and current smoking status were calculated for each time period from information on lifetime smoking history. Marital status, employment status, and educational attainment of each nurse and, if appropriate, of her spouse/partner were included as measures of individual-level socioeconomic status. To control for potential regional differences in PM composition and/or disease risk, we controlled for Census region of residence. Census tract level median income and house value were used to adjust for area-level socioeconomic status. Each potential confounder (or set of confounders) was added to a basic model (adjusted only for age, calendar year, season, and region) 1 at a time to determine the impact on the effect estimates. All confounders were included together in a final multivariable model. We considered a number of a priori potential effect modifiers previously suggested in this cohort and in the wider literature, including region, age, diabetes, family history of MI, BMI, and smoking status.[2,6,8–10,15–17]

Statistical Analyses

Person-months of follow-up were calculated from June 1989 through the end of follow-up, incidence of the specific event

of interest, death, or loss to follow-up, whichever occurred first. Separate time-varying Cox proportional hazards models were used to assess the association of incident CVD, CHD, or stroke with 12-month time-varying averages of each size fraction of PM. Hazard ratios (HRs) and 95% CIs were calculated for each 10 $\mu g/m^3$ increase, after assessing the linearity of each dose-response with cubic regression splines.[18] The dataset was converted to an Anderson–Gill counting process structure with a record for each month that included the appropriate person-time, calculated exposure averages, censoring information, and covariates for that month of follow-up. All models were stratified by age in months and month of study to control for age and temporal effects. To examine effect modification, we calculated stratum-specific effect estimates and examined the statistical significance of any observed effect modification using likelihood ratio tests. In sensitivity analyses, we performed all analyses from 2000 forward, to determine whether the effect estimates were different in the time period where monitoring data on $PM_{2.5}$ was directly available for use in our spatio-temporal prediction models. In the later time period we also conducted sensitivity analyses to examine the impact of longer exposure periods (24-, 60-, and 120-month moving averages). An α level of 0.05 was used to determine statistical significance for main effects, and an α level of 0.0083 (0.05/6 potential modifiers) was used for effect modifiers.

Results

Among 114 537 NHS participants eligible for analysis, 6767 women developed CVD during 1 835 486 person-years of follow-up, and 3878 and 3295 incident cases of CHD and stroke, respectively, were confirmed during this time. A total of 96 058 women were available for analyses starting in 2000 (the first year $PM_{2.5}$ was widely monitored), accounting for 2413 incident CVD cases, 1301 incident CHDs, and 1194 incident strokes during 557 741 years of follow-up. Characteristics of the population throughout both follow-up periods are presented in Table 1. During the full follow-up period, participants were 63.5 (SD=8.5) years old on average, were mainly white, married, and postmenopausal, and were never or former smokers. Characteristics were similar after 2000, with an average participant age of 68.6 (SD=7.3).

The HRs for each outcome for a 10 $\mu g/m^3$ increase in each size fraction of PM are presented in Table 2 for both

Table 4. Multivariable Adjusted HRs and 95% CI for a 10 $\mu g/m^3$ Increase in 12-Month Average PM 1989–2006 With Risk of Incident CVD, CHD, or Stroke, Stratified by Region of Residence

Outcome	Cases	Person-Years	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$
Incident CVD					
Northeast	3368	942 058	1.06 (0.98–1.14)	1.16 (1.00–1.34)	1.06 (0.93–1.21)
Midwest	1160	317 068	0.99 (0.89–1.10)	0.99 (0.83–1.18)	0.98 (0.80–1.21)
West	961	254 336	1.01 (0.95–1.07)	1.03 (0.94–1.13)	0.99 (0.87–1.12)
South	1278	322 024	0.95 (0.81–1.11)	0.92 (0.77–1.10)	1.02 (0.83–1.27)
P-for-interaction			0.51	0.22	0.87
Incident CHD					
Northeast	1996	942 058	1.03 (0.93–1.14)	1.11 (0.92–1.35)	1.01 (0.85–1.20)
Midwest	659	317 068	1.02 (0.88–1.18)	1.06 (0.84–1.34)	1.00 (0.76–1.31)
West	492	254 336	0.99 (0.91–1.08)	0.99 (0.87–1.13)	0.99 (0.83–1.17)
South	731	322 024	0.97 (0.79–1.20)	1.02 (0.81–1.30)	0.92 (0.69–1.22)
P-for-interaction			0.92	0.79	0.96
Incident stroke					
Northeast	1569	942 058	1.06 (0.95–1.19)	1.16 (0.93–1.44)	1.06 (0.87–1.28)
Midwest	576	317 068	0.98 (0.84–1.14)	0.93 (0.72–1.20)	1.03 (0.76–1.38)
West	526	254 336	1.03 (0.95–1.12)	1.09 (0.96–1.23)	0.99 (0.83–1.17)
South	624	322 024	0.97 (0.77–1.22)	0.89 (0.68–1.15)	1.12 (0.83–1.52)
P-for-interaction			0.80	0.27	0.89

Adjusted for age, time period, season, race, smoking status and pack-years, BMI, menopausal status and hormone use, hypercholesterolemia, hypertension, diabetes, family history of MI, and individual- and area-level SES. BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HRs, hazard ratios; MI, myocardial infarction; PM, particulate matter; SES, socioeconomic status.

follow-up periods. In basic models adjusted for age, time period, region, and season, small increases in the risk of incident CVD, CHD, and stroke were observed for all size fractions of PM exposure. These increases only reached statistical significance for the association of PM_{10} with total CVD, and for $PM_{2.5–10}$ with all 3 outcomes in the full period of follow-up. In multivariable models, the results were generally attenuated, and none reached statistical significance. Individual and area-level socioeconomic status appeared to be the most important confounders, and both attenuated the effect estimates for all size fractions. HRs tended to be more elevated for $PM_{2.5}$ in analyses with follow-up starting after 2000, while for $PM_{2.5\ to\ 10}$ HRs were higher in the full period of follow-up.

The 12-, 24-, 60-, and 120-month averages were highly correlated (Table 3) within each size fraction. Within each averaging period, $PM_{2.5}$ and $PM_{2.5–10}$ were weakly correlated ($r\approx0.2$), $PM_{2.5}$ and PM_{10} were moderately correlated ($r\approx0.6$), and PM_{10} and $PM_{2.5–10}$ were strongly correlated ($r\approx0.8$). For CVD, averaging periods >12 months were associated with attenuations in risk for each of the size fractions; the HRs for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ were 1.13, 1.08, 1.04, and 1.02 for the 12-, 24-, 60-, and 120-month exposure windows (Figure). This pattern of attenuations was similar for analyses of stroke, but was less dramatic for analyses of total CHD.

No statistically significant differences in effects were observed across regions in the full period of follow-up (Table 4); however, there was a suggestion of effect modification by region after 2000 (Table 5), with higher HRs observed in the Northeast and South. Multivariable models stratified by selected cardiovascular risk factors are presented in Table 6 for the full follow-up period. For all 3 outcomes, HRs were higher among women with diabetes as compared to those without diabetes, and the test for interaction was statistically significant for the majority of the end points. Among women with diabetes, during the full period of follow-up, the HR of incident total CVD for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.44 (95% CI: 1.23 to 1.68), for $PM_{2.5–10}$ was 1.17 (95% CI: 1.05 to 1.30), and for PM_{10} was 1.19 (95% CI: 1.10 to 1.28). The HRs were higher for stroke (1.66 [95% CI: 1.31 to 2.10] for $PM_{2.5}$, 1.18 [95% CI: 1.01 to 1.38] for $PM_{2.5–10}$, and 1.23 [95% CI: 1.10 to 1.38] for PM_{10}) than for CHD among these women. Effect modification was not consistently detected for the other effect modifiers (age, family history of MI, BMI, smoking status) across size

Table 5. Multivariable Adjusted HRs and 95% CI for a 10 $\mu g/m^3$ Increase in 12-Month Average PM 2000–2006 With Risk of Incident CVD, CHD, or Stroke, Stratified by Region of Residence

Outcome	Cases	Person-Years	PM_{10}	$PM_{2.5–10}$	$PM_{2.5}$
Incident CVD					
Northeast	1189	278 905	1.30 (1.10–1.52)	1.47 (1.09–1.99)	1.44 (1.12–1.86)
Midwest	402	93 823	1.00 (0.80–1.25)	0.91 (0.65–1.29)	1.15 (0.74–1.78)
West	335	78 560	0.95 (0.84–1.06)	0.97 (0.81–1.15)	0.85 (0.67–1.07)
South	487	106 454	1.10 (0.82–1.48)	0.93 (0.69–1.24)	1.34 (0.91–1.98)
P-for-interaction			0.02	0.08	0.02
Incident CHD					
Northeast	665	278 905	1.29 (1.04–1.60)	1.53 (1.02–2.28)	1.39 (0.99–1.96)
Midwest	212	93 823	1.07 (0.78–1.45)	1.05 (0.66–1.67)	1.17 (0.64–2.15)
West	166	78 560	0.87 (0.73–1.03)	0.88 (0.68–1.13)	0.73 (0.52–1.02)
South	258	106 454	1.07 (0.71–1.61)	0.92 (0.62–1.38)	1.30 (0.76–2.22)
P-for-interaction			0.05	0.15	0.05
Incident stroke					
Northeast	568	278 905	1.23 (0.98–1.56)	1.27 (0.81–1.97)	1.42 (0.98–2.05)
Midwest	205	93 823	0.94 (0.68–1.28)	0.78 (0.48–1.27)	1.15 (0.62–2.13)
West	178	78 560	1.03 (0.88–1.20)	1.06 (0.85–1.34)	0.99 (0.73–1.35)
South	243	106 454	1.19 (0.79–1.81)	0.97 (0.64–1.46)	1.44 (0.83–2.50)
P-for-interaction			0.45	0.52	0.44

Adjusted for age, time period, season, race, smoking status and pack-years, BMI, menopausal status and hormone use, hypercholesterolemia, hypertension, diabetes, family history of MI, and individual- and area-level SES. BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HRs, hazard ratios; MI, myocardial infarction; PM, particulate matter; SES, socioeconomic status.

Table 6. Multivariable Adjusted HRs and 95% CI for a 10 μg/m^3 Increase in 12-Month Average PM 1989–2006 With Risk of Incident CVD, CHD, or Stroke, Stratified by Personal Characteristics

Outcome	Cases	Person-Years	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$
Incident CVD					
<70 years old	3429	1 392 830	0.99 (0.93–1.05)	1.00 (0.92–1.09)	0.97 (0.87–1.07)
≥70 years old	3338	442 656	1.06 (1.00–1.13)	1.07 (0.98–1.17)	1.08 (0.97–1.22)
P-for-interaction			0.07	0.17	0.13
Women with diabetes	1512	138 940	1.19 (1.10–1.28)*	1.17 (1.05–1.30)*	1.44 (1.23–1.68)*
Women without diabetes	5255	1 696 546	0.98 (0.94–1.03)*	0.99 (0.93–1.06)*	0.94 (0.86–1.03)*
P-for-interaction			<0.0001*	0.007*	<0.0001*
Family history	2819	612 206	1.05 (0.99–1.11)	1.06 (0.97–1.15)	1.09 (0.97–1.22)
No family history	3948	1 223 280	1.01 (0.96–1.06)	1.01 (0.94–1.09)	1.00 (0.90–1.10)
P-for-interaction			0.24	0.43	0.23
Underweight/normal	2685	791 374	0.99 (0.93–1.05)	0.98 (0.90–1.06)	0.99 (0.88–1.12)
Overweight	2127	583 357	1.04 (0.97–1.11)	1.05 (0.95–1.15)	1.04 (0.91–1.19)
Obese	1737	376 203	1.09 (1.02–1.18)	1.13 (1.02–1.25)	1.12 (0.97–1.30)
P-for-interaction			0.09	0.10	0.41
Never smokers	2459	803 757	1.01 (0.95–1.07)	1.02 (0.93–1.11)	0.99 (0.88–1.12)
Former smokers	2877	765 086	1.05 (0.99–1.12)	1.06 (0.97–1.15)	1.09 (0.97–1.22)
Current smokers	1422	262 982	1.01 (0.92–1.09)	1.00 (0.89–1.12)	1.00 (0.86–1.17)
P-for-interaction			0.47	0.70	0.47
Incident CHD					
<70 years old	2038	1 392 830	0.95 (0.88–1.02)*	0.96 (0.85–1.08)	0.89 (0.77–1.02)
≥70 years old	1840	442 656	1.09 (1.00–1.19)*	1.11 (0.99–1.25)	1.13 (0.97–1.33)
P-for-interaction			0.007*	0.04	0.02
Women with diabetes	1027	138 940	1.12 (1.02–1.23)*	1.14 (1.00–1.30)*	1.20 (0.99–1.46)
Women without diabetes	2851	1 696 546	0.95 (0.89–1.01)*	0.92 (0.84–1.01)*	0.94 (0.84–1.06)
P-for-interaction			0.003*	0.008*	0.03
Family history	1691	612 206	1.04 (0.96–1.12)	1.02 (0.92–1.14)	1.10 (0.95–1.28)
No family history	2187	1 223 280	0.95 (0.89–1.02)	0.94 (0.85–1.04)	0.93 (0.82–1.07)
P-for-interaction			0.09	0.23	0.09
Underweight/normal	1444	791 374	0.95 (0.87–1.03)	0.91 (0.81–1.03)	0.97 (0.82–1.13)
Overweight	1196	583 357	1.01 (0.92–1.11)	1.02 (0.90–1.16)	1.01 (0.84–1.21)
Obese	1078	376 203	1.04 (0.94–1.14)	1.04 (0.91–1.19)	1.08 (0.89–1.30)
P-for-interaction			0.31	0.28	0.68
Never smokers	1309	803 757	1.00 (0.92–1.09)	1.01 (0.90–1.14)	0.97 (0.82–1.14)
Former smokers	1689	765 086	1.00 (0.92–1.08)	0.96 (0.85–1.07)	1.06 (0.91–1.24)
Current smokers	876	262 982	0.97 (0.87–1.08)	0.96 (0.82–1.12)	0.96 (0.78–1.17)
P-for-interaction			0.90	0.77	0.61
Incident stroke					
<70 years old	1552	1 392 830	1.02 (0.94–1.11)	1.04 (0.92–1.18)	1.02 (0.88–1.19)
≥70 years old	1743	442 656	1.04 (0.96–1.13)	1.06 (0.94–1.20)	1.04 (0.88–1.21)
P-for-interaction			0.76	0.77	0.89

Continued

Table 6. Continued

Outcome	Cases	Person-Years	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$
Women with diabetes	659	138 940	1.23 (1.10–1.38)*	1.18 (1.01–1.38)	1.66 (1.31–2.10)*
Women without diabetes	2636	1 696 546	1.03 (0.96–1.09)*	1.08 (0.99–1.18)	0.94 (0.83–1.07)*
P-for-interaction			0.004*	0.33	<0.0001*
Family history	1316	612 206	1.08 (0.99–1.17)	1.13 (1.00–1.26)	1.04 (0.88–1.23)
No family history	1979	1 223 280	1.06 (0.99–1.14)	1.08 (0.98–1.20)	1.06 (0.92–1.22)
P-for-interaction			0.79	0.60	0.83
Underweight/normal	1389	791 374	1.04 (0.96–1.13)	1.07 (0.96–1.20)	1.00 (0.85–1.18)
Overweight	1073	583 357	1.05 (0.95–1.15)	1.06 (0.93–1.21)	1.05 (0.87–1.26)
Obese	772	376 203	1.15 (1.03–1.28)	1.23 (1.06–1.42)	1.15 (0.92–1.43)
P-for-interaction			0.27	0.26	0.61
Never smokers	1266	803 757	1.02 (0.93–1.11)	1.02 (0.91–1.16)	1.02 (0.86–1.21)
Former smokers	1406	765 086	1.11 (1.02–1.21)	1.18 (1.05–1.32)	1.08 (0.91–1.27)
Current smokers	616	262 982	1.05 (0.93–1.18)	1.06 (0.89–1.26)	1.05 (0.83–1.34)
P-for-interaction			0.31	0.20	0.89

Adjusted for age, time period, region, season, race, smoking status and pack-years, BMI, menopausal status and hormone use, hypercholesterolemia, hypertension, diabetes, family history of MI, and individual- and area-level SES as appropriate. BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HRs, hazard ratios; MI, myocardial infarction; PM, particulate matter; SES, socioeconomic status.
**P*-for-interaction below our α level for statistical significance of 0.0083.

fractions. The patterns were similar in post-2000 analyses (Table 7).

Discussion

In this nationwide prospective study, exposures to PM were associated with small, but nonstatistically significant, elevations in incident CVD, CHD, and stroke in this cohort of US women. However, there were consistently statistically significant elevations in risk for almost all PM size fractions and outcomes among women with diabetes. There were also suggestions of effect modification by region of residence, smoking status, obesity, and age, but they were not consistent across outcomes, size fractions, and time periods.

Overall, we observed larger HRs in models restricted to the later time periods, especially for $PM_{2.5}$. This may be due to effect modification by age, as there was a suggestion of higher HRs among older participants in the full follow-up period. These findings may also be due to improvements in our prediction models after 2000. Reductions in measurement error in these models would be expected to lead to increases in the HRs. However, there was overlap in the 95% CIs for the 2 time periods, so it is also possible that our findings of higher risks in the later time period are due to chance.

Our multivariable adjusted results in the full cohort for the full period of follow-up are generally lower than the majority of studies in the literature, including a previous analysis in the NHS cohort.[10,15,19–28] In models among women in the Northeastern and Midwestern regions of the United States, we previously observed multivariable adjusted HRs for CHD incidence of 1.10 (95% CI: 0.94 to 1.29), 1.11 (95% CI: 0.79 to 1.55), and 1.04 (95% CI: 0.82 to 1.32) for each 10 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5}$, and $PM_{2.5-10}$, respectively.[10,15] However, our findings for incident CVD in the later time period are comparable to the equivalent meta-estimate of 10.6% (95% CI 5.4, 16.0) for CVD and $PM_{2.5}$ from all studies of long-term exposures published though January 2013.[2] The results of studies published since then have been more mixed. In the European Study of Cohorts for Air Pollution Effects (ESCAPE), each 5 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a HR=0.99 (95% CI: 0.91 to 1.08) for overall CVD deaths, with similar findings for ischemic heart disease and MI deaths, and for exposures to PM_{10} and $PM_{2.5-10}$.[7] They did observe nonstatistically significantly increased risks of cerebrovascular death of ≈20% with all size fractions of PM. In related analyses of the incidence of acute coronary events, HRs of 1.13 (95% CI: 0.98 to 1.30) per 5 $\mu g/m^3$ increase in $PM_{2.5}$, 1.12 (95% CI: 1.01 to 1.25) per 10 $\mu g/m^3$ increase in PM_{10}, and 1.06 (95% CI: 0.98 to 1.15) per 5 $\mu g/m^3$ increase in $PM_{2.5-10}$ were observed.[8] In an analysis of the American Cancer Society Cancer Prevention Study II (ACS) cohort, each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a HR=1.12 (95% CI: 1.10 to 1.15) for CVD

Table 7. HRs and 95% CI for a 10 μg/m^3 Increase in 12-Month Average PM 2000–2006 With Risk of Incident CVD, CHD, or Stroke, Stratified by Personal Characteristics

Outcome	Cases	Person-Years	PM_{10} Multivariable	$PM_{2.5-10}$ Multivariable	$PM_{2.5}$ Multivariable
Incident CVD					
<70 years old	672	320 469	1.07 (0.93–1.24)	1.08 (0.89–1.32)	1.08 (0.82–1.42)
≥70 years old	1741	237 266	1.04 (0.94–1.14)	1.00 (0.87–1.15)	1.13 (0.95–1.34)
P-for-interaction			0.70	0.48	0.78
Women with diabetes	479	50 349	1.19 (1.02–1.39)	1.15 (0.94–1.40)	1.46 (1.06–2.01)
Women without diabetes	1934	507 392	1.00 (0.92–1.09)	0.98 (0.88–1.09)	1.05 (0.90–1.23)
P-for-interaction			0.05	0.17	0.07
Family history	972	179 039	1.01 (0.90–1.13)	0.97 (0.83–1.13)	1.09 (0.87–1.37)
No family history	1441	378 702	1.06 (0.96–1.16)	1.04 (0.92–1.17)	1.13 (0.94–1.36)
P-for-interaction			0.53	0.51	0.81
Underweight/normal	1008	229 716	1.03 (0.92–1.15)	0.98 (0.85–1.14)	1.16 (0.93–1.43)
Overweight	764	182 467	1.06 (0.94–1.21)	1.03 (0.87–1.22)	1.18 (0.92–1.52)
Obese	587	122 863	1.02 (0.88–1.19)	1.02 (0.84–1.25)	1.04 (0.78–1.40)
P-for-interaction			0.90	0.90	0.81
Never smokers	952	248 739	1.09 (0.98–1.22)	1.12 (0.98–1.29)	1.08 (0.87–1.35)
Former smokers	1119	248 456	1.04 (0.93–1.16)	0.97 (0.84–1.13)	1.23 (0.99–1.51)
Current smokers	340	59 419	0.83 (0.67–1.04)	0.76 (0.56–1.03)	0.91 (0.62–1.33)
P-for-interaction			0.10	0.05	0.38
Incident CHD					
<70 years old	394	320 471	1.07 (0.88–1.31)	1.14 (0.88–1.48)	0.96 (0.66–1.39)
≥70 years old	907	237 270	1.00 (0.87–1.14)	0.95 (0.79–1.16)	1.09 (0.86–1.38)
P-for-interaction			0.53	0.22	0.57
Women with diabetes	309	50 349	1.09 (0.89–1.33)	1.03 (0.78–1.34)	1.31 (0.88–1.96)
Women without diabetes	992	507 392	0.96 (0.85–1.08)	0.94 (0.80–1.10)	0.99 (0.79–1.24)
P-for-interaction			0.29	0.57	0.23
Family history	552	179 039	1.02 (0.87–1.19)	0.95 (0.77–1.17)	1.21 (0.90–1.63)
No family history	749	378 702	0.97 (0.85–1.11)	0.97 (0.81–1.15)	0.96 (0.74–1.24)
P-for-interaction			0.62	0.89	0.24
Underweight/normal	496	229 716	0.98 (0.83–1.15)	0.97 (0.78–1.20)	0.99 (0.73–1.35)
Overweight	411	182 467	0.99 (0.83–1.19)	0.92 (0.73–1.18)	1.15 (0.81–1.62)
Obese	351	122 863	1.01 (0.83–1.23)	0.96 (0.74–1.26)	1.13 (0.77–1.65)
P-for-interaction			0.97	0.96	0.79
Never smokers	478	248 739	1.10 (0.94–1.28)	1.15 (0.95–1.40)	1.03 (0.75–1.42)
Former smokers	620	248 456	0.93 (0.79–1.08)	0.81 (0.66–1.01)	1.15 (0.86–1.52)
Current smokers	202	59 419	0.90 (0.68–1.19)	0.89 (0.61–1.28)	0.88 (0.53–1.45)
P-for-interaction			0.23	0.05	0.65
Incident stroke					
<70 years old	300	320 471	1.08 (0.87–1.34)	1.02 (0.75–1.38)	1.27 (0.84–1.91)
≥70 years old	894	237 270	1.07 (0.94–1.22)	1.04 (0.86–1.25)	1.16 (0.92–1.47)
P-for-interaction			0.92	0.89	0.72

Continued

Table 7. Continued

Outcome	Cases	Person-Years	PM_{10}	$PM_{2.5-10}$	$PM_{2.5}$
			Multivariable	Multivariable	Multivariable
Women with diabetes	194	50 349	1.31 (1.05–1.65)	1.29 (0.97–1.73)	1.64 (1.00–2.69)
Women without diabetes	1000	507 392	1.04 (0.93–1.16)	1.01 (0.87–1.17)	1.13 (0.91–1.40)
P-for-interaction			0.06	0.13	0.17
Family history	457	179 039	0.98 (0.83–1.16)	0.99 (0.79–1.23)	0.95 (0.68–1.32)
No family history	737	378 702	1.14 (1.01–1.29)	1.10 (0.93–1.29)	1.37 (1.07–1.76)
P-for-interaction			0.15	0.45	0.08
Underweight/normal	542	229 716	1.06 (0.92–1.23)	0.98 (0.80–1.19)	1.33 (1.00–1.78)
Overweight	387	182 467	1.15 (0.97–1.37)	1.15 (0.93–1.44)	1.24 (0.87–1.76)
Obese	254	122 863	1.02 (0.81–1.28)	1.06 (0.79–1.43)	0.93 (0.60–1.46)
P-for-interaction			0.66	0.54	0.42
Never smokers	494	248 739	1.10 (0.94–1.27)	1.10 (0.90–1.33)	1.16 (0.85–1.58)
Former smokers	549	248 456	1.15 (0.99–1.33)	1.12 (0.93–1.36)	1.32 (0.98–1.77)
Current smokers	150	59 419	0.75 (0.54–1.06)	0.62 (0.38–1.00)	0.93 (0.52–1.65)
P-for-interaction			0.08	0.07	0.55

Adjusted for age, time period, region, season, race, smoking status and pack-years, BMI, menopausal status and hormone use, hypercholesterolemia, hypertension, diabetes, family history of MI, and individual- and area-level SES as appropriate. BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HRs, hazard ratios; MI, myocardial infarction; PM, particulate matter; SES, socioeconomic status.

mortality, with similar effect sizes for ischemic heart disease and cerebrovascular mortality.[16]

Previously in the NHS, we observed suggestions of effect modification of our $PM_{2.5}$ results by a number of cardiovascular risk factors, although none of the modifiers reached statistical significance (defined as $P<0.05$). In analyses of $PM_{2.5}$, higher HRs for total CHD were observed among women with diabetes, those with a family history of MI, individuals with hypercholesterolemia or hypertension, former and never smokers, and the obese.[15] A few recent long-term studies have systematically assessed effect modification to identify susceptible subpopulations with mixed results. In both ESCAPE analyses, no effect modification was observed by smoking status, BMI, or hypertension; diabetes was not considered as an effect modifier.[7,8] Recent results from the Agricultural Health Study showed elevated risks of CVD mortality for increasing $PM_{2.5}$ exposures only among male participants.[9] Effect modification by BMI was observed, with the highest risks among men with a BMI $\geq$26.5 kg/m^2. In the ACS, no statistically significant effect modification was observed by baseline report of diabetes, hypertension or existing heart disease.[16] A recent review of effect modification in studies of the effects of short-term PM exposures found strong evidence of effect modification by age, with higher risks among older individuals, weak or limited evidence of effect modification by sex and socioeconomic status, and no effect modification by race.[17] Short-term studies have also examined effect modification by diabetes, and most have suggested that individuals with diabetes are a susceptible subpopulation.[3,4,29–34] Therefore, although there is consistent evidence that individuals with diabetes are particularly vulnerable to the cardiovascular effects of acute exposures to air pollution, our study is one of the first to demonstrate high risks of CVD among individuals with diabetes with long-term exposures to PM.

Differences in susceptibility, especially among individuals with diabetes, have also been reported in studies designed to elucidate the biological mechanisms, typically inflammation, underlying the adverse health effects of PM. The most comparable studies, in terms of the populations studied and the $PM_{2.5}$ exposure averaging times used, have focused on the effects of $PM_{2.5}$ on C-reactive protein (CRP). In the longitudinal Study of Women's Health Across the Nation, associations between $PM_{2.5}$ averaged over the previous 12 months and CRP were strongest among women with diabetes, with a 72.1% increase (95% CI: 2.9 to 187.8) in CRP for each 10 μg/m^3 increase in $PM_{2.5}$ in the full study population and a 301% increase (no confidence interval provided) in CRP among the oldest participants with diabetes (aged 50.5 to 55 years of age at the start of the study).[35] In the German Heinz Nixdorf Recall Study, increases in annual average $PM_{2.5}$ were associated with increases in CRP in only male participants. However, each

3.91 μg/m^3 increase in $PM_{2.5}$ was associated with an 82.6% increase (95% CI: 1.1 to 230.3) in CRP among women with diabetes, which was the largest increase observed among a number of subgroups examined.[36]

Few studies have examined the impacts of different exposure averaging windows. In our previous work in the NHS, our findings for all size fractions were generally consistent for exposure averaging times of 12 to 48 months.[10,15] The HRs were most consistent in analyses of PM_{10} and $PM_{2.5\ to\ 10}$. This is in contrast to our current findings that show lower HRs for the 60- and 120-month exposure averaging times compared to the 12- and 24-month averages. However, the high correlations in exposures across time windows make it difficult to determine whether these differences are solely due to chance or are related to true differences in risk.

The limitations of this study should be noted. The NHS predominantly comprises middle-aged and elderly white women who at one time were nurses. Therefore, our results may not be generalizable to men or to more racially or socioeconomically diverse populations. Although we used a sophisticated spatio-temporal model to estimate ambient PM concentrations at the home addresses of each participant, measurement error may still be present. We do not have information on time-activity patterns, or housing characteristics that may influence the infiltration of ambient PM. Additionally, the lack of available monitoring information on $PM_{2.5}$ prior to 1999 and the need to estimate $PM_{2.5\ to\ 10}$ concentrations by subtraction for the full time period could also lead to exposure misclassification. Although we had time-varying information on a number of confounders, residual confounding is still always a concern even though validation studies suggest accurate reporting in this group.[37] The issue of residual confounding is also raised by our observation of confounding by socioeconomic status, both individual and area level; our inability to control for small-scale spatial autocorrelation; or spatial patterns in our selected confounders and effect modifiers, including the potentially strong spatial patterns of diabetes prevalence in the United States.

This study also has notable strengths, including extensive follow-up, a large number of well-validated cases of CVD, as well as close to 20 years of monthly ambient PM predictions. Compared to a number of studies with only mortality data, we had the ability to examine incident cases. Finally, we have time-varying information available on a variety of confounders and effect modifiers of interest, which allowed us to evaluate the importance of effect modification independent of key cardiovascular risk factors.

In conclusion, in this nationwide population of middle-aged and older women, exposures to PM were associated with small, but non–statistically significant increases in the risk of incident cardiovascular disease. This risk was elevated and statistically significant among women with diabetes. There also were suggestions of effect modification by age and region; however, these were not consistent across PM size fractions, time periods of follow-up, or outcomes. Overall, this study adds to the literature on chronic exposures to air pollution with cardiovascular outcomes, and adds to the limited body of knowledge identifying especially susceptible populations.

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Disclosures

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References

1. Pope CA III, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc*. 2006;56:709–742.
2. Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, Kaufman JD. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ Health*. 2013;12:43.
3. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*. 2004;109:2655–2671.
4. Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121:2331–2378.
5. Burnett RT, Pope CA III, Ezzati M, Olives C, Lim SS, Mehta S, Shin HH, Singh G, Hubbell B, Brauer M, Anderson HR, Smith KR, Balmes JR, Bruce NG, Kan H, Laden F, Pruss-Ustun A, Turner MC, Gapstur SM, Diver WR, Cohen A. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. *Environ Health Perspect*. 2014;122:397–403.
6. Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, Wolf K, Samoli E, Fischer P, Nieuwenhuijsen M, Vineis P, Xun WW, Katsouyanni K, Dimakopoulou K, Oudin A, Forsberg B, Modig L, Havulinna AS, Lanki T, Turunen A, Oftedal B, Nystad W, Nafstad P, De Faire U, Pedersen NL, Ostenson CG, Fratiglioni L, Penell J, Korek M, Pershagen G, Eriksen KT, Overvad K, Ellermann T, Eeftens M, Peeters PH, Meliefste K, Wang M, Bueno-de-Mesquita B, Sugiri D, Kramer U, Heinrich J, de Hoogh K, Key T, Peters A, Hampel R, Concin H, Nagel G, Ineichen A, Schaffner E, Probst-Hensch N, Kunzli N, Schindler C, Schikowski T, Adam M, Phuleria H, Vilier A, Clavel-Chapelon F, Declercq C, Grioni S, Krogh V, Tsai MY, Ricceri F, Sacerdote C, Galassi C, Migliore E, Ranzi A, Cesaroni G, Badaloni C, Forastiere F, Tamayo I, Amiano P, Dorronsoro M, Katsoulis M, Trichopoulou A, Brunekreef B, Hoek G. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet*. 2014;383:785–795.
7. Beelen R, Stafoggia M, Raaschou-Nielsen O, Andersen ZJ, Xun WW, Katsouyanni K, Dimakopoulou K, Brunekreef B, Weinmayr G, Hoffmann B,

Wolf K, Samoli E, Houthuijs D, Nieuwenhuijsen M, Oudin A, Forsberg B, Olsson D, Salomaa V, Lanki T, Yli-Tuomi T, Oftedal B, Aamodt G, Nafstad P, De Faire U, Pedersen NL, Ostenson CG, Fratiglioni L, Penell J, Korek M, Pyko A, Eriksen KT, Tjonneland A, Becker T, Eeftens M, Bots M, Meliefste K, Wang M, Bueno-de-Mesquita B, Sugiri D, Kramer U, Heinrich J, de Hoogh K, Key T, Peters A, Cyrys J, Concin H, Nagel G, Ineichen A, Schaffner E, Probst-Hensch N, Dratva J, Ducret-Stich R, Vilier A, Clavel-Chapelon F, Stempfelet M, Grioni S, Krogh V, Tsai MY, Marcon A, Ricceri F, Sacerdote C, Galassi C, Migliore E, Ranzi A, Cesaroni G, Badaloni C, Forastiere F, Tamayo I, Amiano P, Dorronsoro M, Katsoulis M, Trichopoulou A, Vineis P, Hoek G. Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. *Epidemiology*. 2014;25:368–378.

8. Cesaroni G, Forastiere F, Stafoggia M, Andersen ZJ, Badaloni C, Beelen R, Caracciolo B, de Faire U, Erbel R, Eriksen KT, Fratiglioni L, Galassi C, Hampel R, Heier M, Hennig F, Hilding A, Hoffmann B, Houthuijs D, Jockel KH, Korek M, Lanki T, Leander K, Magnusson PK, Migliore E, Ostenson CG, Overvad K, Pedersen NL, Juha JP, Penell J, Pershagen G, Pyko A, Raaschou-Nielsen O, Ranzi A, Ricceri F, Sacerdote C, Salomaa V, Swart W, Turunen AW, Vineis P, Weinmayr G, Wolf K, de Hoogh K, Hoek G, Brunekreef B, Peters A. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ*. 2014;348:f7412.
9. Weichenthal S, Villeneuve PJ, Burnett RT, van Donkelaar A, Martin RV, Jones RR, DellaValle CT, Sandler DP, Ward MH, Hoppin JA. Long-term exposure to fine particulate matter: association with nonaccidental and cardiovascular mortality in the Agricultural Health Study Cohort. *Environ Health Perspect*. 2014;122:609–615.
10. Puett RC, Schwartz J, Hart JE, Yanosky JD, Speizer FE, Suh H, Paciorek CJ, Neas LM, Laden F. Chronic particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. *Am J Epidemiol*. 2008;168:1161–1168.
11. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981;12:I13–I44.
12. Yanosky JD, Paciorek CJ, Laden F, Hart JE, Puett RC, Liao D, Suh HH. Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. *Environ Health*. 2014;13:63.
13. Spengler JD, Koutrakis P, Dockery DW, Raizenne M, Speizer FE. Health effects of acid aerosols on North American children: air pollution exposures. *Environ Health Perspect*. 1996;104:492–499.
14. Suh HH, Nishioka Y, Allen GA, Koutrakis P, Burton RM. The metropolitan acid aerosol characterization study: results from the summer 1994 Washington, D.C. field study. *Environ Health Perspect*. 1997;105:826–834.
15. Puett RC, Hart JE, Yanosky JD, Paciorek CJ, Schwartz J, Suh H, Speizer FE, Laden F. Chronic fine and coarse particulate exposure, mortality and coronary heart disease in the Nurses' Health Study. *Environ Health Perspect*. 2009;117:1697–1701.
16. Pope CA, Turner MC, Burnett R, Jerrett M, Gapstur SM, Diver WR, Krewski D, Brook RD. Relationships between fine particulate air pollution, cardiometabolic disorders and cardiovascular mortality. *Circ Res*. 2014;116:108–115.
17. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *Am J Epidemiol*. 2013;178:865–876.
18. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8:551–561.
19. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect*. 2012;120:965–970.
20. Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287:1132–1141.
21. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356:447–458.
22. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Jerrett M, Hughes E, Armstrong B, Brunekreef B. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect*. 2008;116:196–202.
23. Puett RC, Hart JE, Suh H, Mittleman M, Laden F. Particulate matter exposures, mortality, and cardiovascular disease in the health professionals follow-up study. *Environ Health Perspect*. 2011;119:1130–1135.
24. Gan WQ, Koehoorn M, Davies HW, Demers PA, Tamburic L, Brauer M. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environ Health Perspect*. 2011;119:501–507.
25. Hart JE, Garshick E, Dockery DW, Smith TJ, Ryan L, Laden F. Long-term ambient multipollutant exposures and mortality. *Am J Respir Crit Care Med*. 2011;183:73–78.
26. Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, Khan S, Atari DO, Jerrett M, Pope CA, Brauer M, Brook JR, Martin RV, Stieb D, Burnett RT. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ Health Perspect*. 2012;120:708–714.
27. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *Am J Respir Crit Care Med*. 2011;184:828–835.
28. Cesaroni G, Badaloni C, Gariazzo C, Stafoggia M, Sozzi R, Davoli M, Forastiere F. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*. 2013;121:324–331.
29. Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? *Am J Respir Crit Care Med*. 2001;164:831–833.
30. Villeneuve PJ, Johnson JY, Pasichnyk D, Lowes J, Kirkland S, Rowe BH. Short-term effects of ambient air pollution on stroke: who is most vulnerable? *Sci Total Environ*. 2012;430:193–201.
31. Kloog I, Coull BA, Zanobetti A, Koutrakis P, Schwartz JD. Acute and chronic effects of particles on hospital admissions in New-England. *PLoS One*. 2012;7:e34664.
32. D'Ippoliti D, Forastiere F, Ancona C, Agabiti N, Fusco D, Michelozzi P, Perucci CA. Air pollution and myocardial infarction in Rome: a case-crossover analysis. *Epidemiology*. 2003;14:528–535.
33. Zeka A, Zanobetti A, Schwartz J. Individual-level modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol*. 2006;163:849–859.
34. Filleul L, Rondeau V, Cantagrel A, Dartigues JF, Tessier JF. Do subject characteristics modify the effects of particulate air pollution on daily mortality among the elderly? *J Occup Environ Med*. 2004;46:1115–1122.
35. Ostro B, Malig B, Broadwin R, Basu R, Gold EB, Bromberger JT, Derby C, Feinstein S, Greendale GA, Jackson EA, Kravitz HM, Matthews KA, Sternfeld B, Tomey K, Green RR, Green R. Chronic $PM_{2.5}$ exposure and inflammation: determining sensitive subgroups in mid-life women. *Environ Res*. 2014;132:168–175.
36. Hoffmann B, Moebus S, Dragano N, Stang A, Mohlenkamp S, Schmermund A, Memmesheimer M, Brocker-Preuss M, Mann K, Erbel R, Jockel KH. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environ Health Perspect*. 2009;117:1302–1308.
37. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol*. 1986;123:894–900.